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# The measurement of oestradiol, progesterone, LH, FSH and hCG for assisted reproduction: A comparison of the Siemens Centaur CP and Roche e411 automated analysers

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## ABSTRACT

**Objective:** To compare the results of two automated analysers by measuring reproductive hormones using the same quality control. **Methods:** Results obtained by the Roche Cobas e411 automated analyser in a specialised fertility clinic were compared to the Siemens Centaur CP for the reproductive hormones oestradiol, progesterone, LH, FSH and hCG. **Results:** Commercially-available quality control (QC) samples showed significant differences between the two assays for all five hormones at one or more levels. In clinical samples, the range of concentrations encountered was similar to the QC samples for LH and FSH but much higher for oestradiol, progesterone, and hCG showing the limitations of such QC samples in a specialised fertility setting when they are intended for general pathology use. There was a high degree of correlation for all hormones (all  $r > 0.985$ ) and a gradient close to 1 for all, except for hCG when the Siemens analyser read  $\geq 1\,000$  IU/L ( $r = 1.209$ ) and this is reflected in a large mean bias ( $-2\,647.9$  IU/L) and coefficient of repeatability ( $11\,690.0$  IU/L) when using a Bland-Altman plot. **Conclusions:** Despite an overall agreement between the two assay platforms for progesterone, LH and FSH, small differences between the two analysers in the concentrations of oestradiol and hCG as encountered in natural ovarian cycles or at the time of pregnancy testing may require a redefinition of clinical cut-offs.

## 1. Introduction

The measurement of reproductive hormones plays an important role in the monitoring of fertility treatment cycles and early pregnancy [1, 2]. Clinical decisions for the daily management of patients can be made promptly by clinicians due to the rapid determination of hormone concentrations by modern day methods. However, it is well known that differences in numerical values exist

between different commercial assays when analysing the same sample [3–5]. Such differences can occur through a wide range of factors including antibody specificity, choice of standard preparations, and optimisation of the assay over defined analyte ranges [3, 6]. The availability of a variety of automated analysers has prompted systematic evaluations in the past [7–9], to help laboratories make informed decisions on their choice of equipment, and for practitioners to make informed clinical decisions when interpreting results.

The aims of the present study were to (a) compare the results of two automated analysers by measuring reproductive hormones using the same quality control (QC) and clinical samples, and (b) assess the merits of using both machines in a routine clinical service.

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## 2. Materials and methods

### 2.1. Patients and samples

Blood was collected in BD Vacutainer® SST™ serum separation tubes (Vacutainer; Becton Dickinson) from women as part of their routine fertility investigation or management, allowed to clot at room temperature and then centrifuged at 1 300 g for 4 minutes. Hormones were measured within 6 hours of collection.

### 2.2. Hormone assays

Serum samples were analysed initially on the Centaur CP automated analyser (Siemens; Bayswater, Victoria, Australia) and the results forwarded to the clinician. The samples were then re-analysed on the Cobas e411 automated analyser (Roche; Roche Diagnostics Australia Pty Ltd Perth, Western Australia) on the same day to avoid sample storage as a variable. Five reproductive hormones, namely oestradiol, progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and human chorionic gonadotrophin (hCG), were measured in singlicate. Samples for hCG measurement on the Siemens Centaur were diluted if the initial concentration was  $>1\,000$  IU/L and diluted on the Roche Cobas e411 if the initial concentration was  $>10\,000$  IU/L. Internal QC samples (Lyphochek® Immunoassay Plus Control Trilevel; Bio-Rad Laboratories, Irvine, CA, USA) were run daily to confirm the assays on the Centaur CP and Roche Cobas e411 were measuring within acceptable limits.

### 2.3. Statistical analysis

Comparisons of the hormone concentrations for each QC sample was made using the paired *t*-test, and differences considered significant if  $P < 0.05$ . Patient samples were compared using Pearson's correlation (correlation coefficient and trend line) and Bland–Altman plots (mean bias and coefficient of repeatability) [10].

## 3. Results

### 3.1. Assay characteristics

Differences exist between the two assay systems in the underlying technology, with the Siemens tests being competitive chemiluminescent immunoassays whereas the Roche assay system uses electrochemiluminescence (ECL) technology. The operational details of the two assay systems are shown in Table 1. The assay time was very similar between the two assays for all analytes, varying between 15 and 19.7 minutes to obtain a result. The Centaur CP used slightly larger sample volumes for all but the progesterone assay. The Cobas e411 had a lower concentration included on the standard curve for all assays apart for LH, and a higher top standard for oestradiol and hCG.

### 3.2. Quality control samples

The hormone concentrations measured in the three levels of QC material are shown in Table 2. There were significant differences between the two assays for all five hormones but not in a consistent manner. The Roche assay gave lower oestradiol and FSH results for the medium and high level QC samples but higher FSH concentrations at the low level QC. The Roche progesterone and hCG assays were lower compared to the Siemens assays at the low QC level but higher at the high level. The two LH assays were comparable for the medium and high level QC samples, with the Roche being higher only at the low QC level compared to the Siemens machine.

### 3.3. Clinical samples

The summary data for the patient samples is shown in Table 3. The range of concentrations encountered was similar to the range of the QC samples for LH and FSH. However, the patient samples had a much higher range for oestradiol, progesterone and hCG showing the limitations of such QC samples in a specialised fertility setting when they are intended for general pathology use. There was a high degree of correlation for all hormones (all  $r > 0.985$ ), and a gradient close to 1 for all except hCG  $\geq 1\,000$  IU/L which was 1.209. The similarity between the two assay platforms for oestradiol, progesterone, LH and FSH is reflected in the relatively low mean bias and coefficients of repeatability. However, the skewed gradient for hCG when the Siemens machine measures  $\geq 1\,000$  IU/L shows the Roche analyser to give lower values compared to the Siemens analyser and results in a large mean bias and coefficient of repeatability using a Bland–Altman plot.

Based upon the gradient of the correlation trendline and intercept shown in Table 3, comparative values for the two systems are shown in Table 4 for a range of clinical scenarios for all five hormones. This takes into account both the correlation between the assays and the critical concentration of hormone. Threshold concentrations for progesterone to identify spontaneous luteinisation [11] and luteal insufficiency were very similar between the two assays, as were LH to confirm pituitary suppression with GnRH analogues, and FSH as a marker for reduced ovarian reserve. Oestradiol at lower concentrations, as encountered in natural ovarian cycles, were slightly different but not at higher levels such as seen in cases of ovarian hyperstimulation in IVF cycles. The detection of pregnancy by the measurement of hCG is an important assessment made at the end of a treatment cycle, with large implications to patients. Using the Roche analyser would require a revised cut-off closer to 20 IU/L if the same criteria of clinical management were to be maintained.

Simple calculations of coefficients of variation based upon the mean and standard deviation of repeat between–batch analysis of QC material (Table 2) showed good reproducibility for most assays but with the greatest variability ( $>8.0\%$ ) being seen with low concentrations of oestradiol, progesterone and LH measured with the Siemens analyser. Of the 15 sets of results, ie 5 hormones at 3 levels, the Roche analyser had lower CV's in 66.7 % (10/15).

**Table 1**

Details of the assays used on the Siemens Centaur CP and Roche Cobas e411 automated analysers.

Hormone	Centaur CP				Cobas e411			
	Sample size ( $\mu$ L)	Standard curve	Assay time (min)	Reference preparation	Sample size ( $\mu$ L)	Standard curve	Assay time (min)	Reference preparation
Oestradiol	80	43.6–11 010.0 pmol/L	16.0	—	35	18.4–15 781.0 pmol/L	18	—
Progesterone	20	0.67–190.80 nmol/L	19.7	—	30	0.095–191.000 nmol/L	18	—
LH	50	0.07–200.00 IU/L	15.0	2 <sup>nd</sup> WHO 80/552	20	0.10–200.00 IU/L	18	2 <sup>nd</sup> WHO 80/552
FSH	100	0.3–200.0 IU/L	15.0	2 <sup>nd</sup> WHO 78/549	40	0.1–200.0 IU/L	18	2 <sup>nd</sup> WHO 78/549
hCG	50	2.0–1 000.0 IU/L	15.0	3 <sup>rd</sup> IRP 75/537	10	0.1–10 000.0 IU/L	18	4 <sup>th</sup> IRP 75/589

**Table 2**The internal quality control data obtained when analysing the BioRad Lyphochek<sup>®</sup> Immunoassay Plus Control Trilevel on both the Siemens Centaur CP and the Roche e411.

Hormone	Concentration (CV)					
	Siemens			Roche		
	Low	Medium	High	Low	Medium	High
Oestradiol (pmol/L) (n=11)	350.5±18.7 (8.2%)	894.7±17.1 (6.3%)	2 196.9±34.2 (5.2%)	328.2 ± 6.6 (6.7%)	701.8 ± 11.1 ** (5.2%)	1 514.0 ± 19.4 ** (4.2%)
Progesterone (nmol/L)(n=12)	2.8±0.1 (14.2%)	25.9±0.3 (4.1%)	60.4±1.0 (5.9%)	1.2±0.0 ** (5.0%)	29.3±0.2 ** (2.1%)	84.9±0.9 ** (3.8%)
LH (IU/L)(n=13)	1.3±0.0 (8.6%)	19.3±0.2 (3.4%)	68.3±0.9 (4.8%)	1.5±0.0 ** (4.2%)	19.4±0.2 (3.4%)	66.8±0.6 (3.2%)
FSH (IU/L)(n=18)	5.4±0.1 (4.4%)	27.5±0.3 (4.1%)	56.8±0.6 (4.1%)	6.1±0.1 ** (4.4%)	26.6±0.3 * (4.1%)	50.5±0.5 * (4.4%)
hCG (IU/L)(n=14)	6.7±0.1 (6.4%)	21.1±0.2 (2.7%)	175.8±1.9 (4.0%)	5.6±0.1 ** (4.0%)	20.9±0.3 (4.8%)	184.3±1.9 * (3.8%)

Results are expressed as the mean ± sem, and the coefficient of variation (CV), \**P*<0.05; \*\**P*<0.01.**Table 3**

The relationship of results for routine clinical samples obtained on the Siemens Centaur CP and Roche Cobas e411 automated analysers.

Hormone	Number samples	Sample range	Comparison			Difference	
			<i>r</i>	gradient	intercept	Mean bias	Coefficient of repeatability
Oestradiol	138	47.8–16 689.0 pmol/L	0.986	1.001	100.2 pmol/L	−101.1 pmol/L	703.5 pmol/L
Progesterone	133	0.6–516.8 nmol/L	0.998	1.051	0.2 nmol/L	−1.4 nmol/L	10.2 nmol/L
LH	134	0.5–67.6 IU/L	0.994	1.009	0.5 IU/L	−0.6 IU/L	2.5 IU/L
FSH	105	1.9–67.6 IU/L	0.996	1.074	0.3 IU/L	−0.4 IU/L	1.9 IU/L
hCG (<1000IU/L)	66	1.9–947 IU/L	0.996	0.952	−4.6 IU/L	+1.2 IU/L	50.0 IU/L
hCG (≥1000IU/L)	48	1 250–105 400 IU/L	0.987	1.209	−836.7 IU/L	−2 647.9 IU/L	11 690.0 IU/L

The descriptive statistics were obtained by comparison and Bland–Altman plots.

**Table 4**

A comparison of the Roche Cobas e411 automated analyser with the Siemens Centaur CP at critical decision levels based on results with the Centaur CP.

Hormone	Clinical relevance	Threshold value Siemens assay	Comparative value Roche assay
Oestradiol			
–Natural cycle	Mid-cycle	880 pmol/L [18]	981.1 pmol/L
–IVF cycle	Ovarian hyperstimulation syndrome	12 850 pmol/L [19]	12 963.1 pmol/L
Progesterone			
–Follicular phase (IVF)	Spontaneous luteinisation	5.1 nmol/L [11]	5.6 nmol/L
–Luteal phase (Natural cycle)	Luteal insufficiency	30 nmol/L [20]	31.7 nmol/L
LH			
–IVF cycle with GnRHa	Pituitary suppression	2 IU/L [21]	2.5 IU/L
FSH			
–Natural cycle	Reduced ovarian reserve	10 IU/L [22]	11.0 IU/L
hCG			
–Pregnancy test	Biochemical evidence of implantation	25 IU/L [23]	19.2 IU/L

#### 4. Discussion

Whilst much is written about the endocrinology of reproduction, it is important to pay attention to the methods used to measure the hormone concentrations because clinical decisions are made when hormone concentrations cross set levels, such as those shown in Table 4. This means the numerical values obtained with the assay methods at those levels are more important. A number of other studies have compared the results obtained with different assays and revealed major differences [7–9], demonstrating that the use of automated analysers does not diminish the efforts needed to reduce variability between laboratories using different methods [4]. The current study has aimed to compare the performance of the Roche Cobas e411 analyser with that of the Siemens Centaur CP. The two assay systems use different end-points, with the Siemens system using chemiluminescence and the Roche system using electrochemiluminescence (ECL).

Good practice requires that QC samples be run daily to ensure laboratories can confirm that the assays are stable and that between-batch variability is kept to a minimum. A number of commercially-available QC samples are available, and the present study used the tri-level Lyphochek<sup>®</sup> Immunoassay Plus Control (Bio-Rad Laboratories, Irvine, CA, USA). However, the limitation in a specialised medical setting of using QC material that is designed for general pathology. Whilst the QC material had LH and FSH levels which mirrored that of the clinical samples, the range of progesterone and oestradiol concentrations was much higher in clinical samples because of the use of ovarian stimulation within the IVF programme. Similarly, hCG levels were much higher in the clinical samples because of the extended period of pregnancy monitoring preferred by the medical practitioners managing fertility patients.

Assays require the use of authentic compounds to act as a standard against which the unknown concentration in a sample can be calculated. The complex tertiary structure of protein hormones has meant that standards have been made from hormone extracted from biological samples or specimens and then confirmed as internationally-agreed standards by a recognised authority. Use of the same standards is important in minimising variability between methods due to differences in calibration [12], as differences can occur due to charge heterogeneity [6]. Standards used in the two assay systems for LH, FSH and hCG are summarised in Table 1. Both systems calibrate the LH assays using the second International Standard 80/552 of pituitary LH [13]. At first sight it would appear that different standards are being used to calibrate the FSH and hCG assays, but this is not the case. The 2<sup>nd</sup> FSH reference preparation 78/549 is now exhausted (see NIBSC 94/632 Instructions for use [version 5.0, Dated 23/09/2010]), and so an interim batch was made from material contained within the master ampoules and made available as 94/632; they are therefore two different batches made from the same master preparation. Similarly, the hCG 3<sup>rd</sup> International Standard 75/537 was almost exhausted in 1999 (see NIBSC 75/589 Instructions for use [Version 3.0, Dated 30/11/2007]) and a second batch of ampoules was therefore made from the same bulk preparation used to make 75/537, and this second batch was labelled 75/589 [14].

Oestradiol and progesterone are the main steroid hormones measured to monitor ovarian function within fertility clinics. Previous workers have shown results from an external quality assurance scheme to reveal that there are considerable bias differences for both hormones between other methods[7]. Oestradiol results from different methods have also been shown previously to differ for samples collected within IVF programmes although the clinical interpretation was similar[8, 15]. Samples with low levels of oestrogen can require a redefinition of clinical cut-off values [16], and this is consistent with the present study where the greatest difference was at the low end of the standard curve with levels generally associated with natural ovarian cycles. Variability between methods measuring oestradiol concentrations in the physiological range has been confirmed[9], and the practical problems and limitations of oestradiol assays being used over such a wide dynamic range to cover a large number of clinical scenarios has been noted[17].

In summary, the present study has shown that commercial QC samples designed for use by general pathology laboratories do not always reflect the range of concentrations encountered in a specialist fertility setting. Care is always required by laboratories considering a change in methodology and clinicians reviewing results generated by different laboratories, but the Siemens centaur CP and Roche Cobas e411 gave good agreement for most of the assays. Areas of difference, such as that seen at low concentrations of oestradiol and hCG and high concentrations of hCG, mean that consideration should be given to the need for continuity of results held in a database and the possible redefinition of clinical cut-offs where appropriate.

#### Declare of interest statement

We declare that we have no conflict of interest.

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